IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: GOPFERICH et al.	Group Art Unit: 1618
Serial No: 10/019,797	Examiner: Hartley, Michael G
Filed: July 26, 2002	
For: Biodegradable Block Copolymers with Modifiable Surface	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AFFIDAVIT OF JAYASREE VASUDEVAN, Ph.D.

Dear Madam/Sir:

I, Jayasree Vasudevan, hereby declare as follows:

1. I received a Bachelor of Science degree in Mathematics, Physics and Chemistry in 1987 (with first class honors), and a Masters of Science degree in Chemistry in 1989 (with first class honors) from Osmania University, Hyderabad, India. In 1994 I received a Ph.D. in Chemistry from the Indian Institute of Chemical Technology, Hyderabad, India, where my thesis project concerned the synthesis of biologically active compounds.

2. I was granted a post-doctoral fellowship at Rutgers University from December 1994 to December 1996.

3. In September 1997 I joined the Retinoid Research group at Allergan, Inc. in Irvine, California as a Scientist in Medicinal Chemistry. I worked in the Retinoid Research group at Allergan, Inc. 1997 to April 2004, during which time I held the positions of Scientist, Senior Scientist, and Principal Scientist, and was a member of the Research Management Committee, of the Allergan-Cytochroma research collaboration (May 1999-May 2004) that led to identification of a P450RAI inhibitor lead candidate for dermatological disease treatment.

4. In May 2004 I joined Vitae Pharmaceuticals as Senior Research Scientist, where I continued retinoid-related work, with duties including Management of API and drug product manufacturing CROs for Phase 1/2a IND enabling toxicology studies and early phase clinical studies; Primary

Preparation of pre-IND briefing packages and CMC sections for Phase 1/2a IND and IMPD, and CMC contact for interface with the FDA for both drug substance and drug product at the pre-IND and Phase 1/2a IND stage.

5. In May 2007 I joined NuRx Pharmaceuticals, where I continued working on the development of an RXR agonist and an RAR subtype selective agonist in the areas of dermatology and oncology as it pertained to scale up and procurement of drug substances and drug products and coordination of chemistry related development activities, including Management of API and drug product manufacturing CROs for early phase clinical studies. I was also involved in the preparation of CMC sections for two Phase 1/2a INDs. I managed the intellectual property portfolio based on overall company goals at NuRx.

6. In June 2008 I took and passed the examination for admission to practice before the United States Patent and Trademark Office, and received Registration Number 62864. I was employed as an independent contractor, continuing my chemistry research and development related work with NuRx Pharmaceuticals on a part-time basis. In September 2009 I became employed full-time as an independent contractor practicing as a patent agent with the law firm of Stout, Uxa, Buyan & Mullins, LLP.

7. I have reviewed the Advisory Action (AA) in this matter dated May 19, 2010 and the Final Office Action (FOA) of January 21, 2010. I understand that the pending claims of the present patent application are directed in part to a linear block copolymer. The copolymer comprises the structure c2)-b)-c1)-a). In this copolymer, a) is a hydrophobic biodegradable polymer a), selected from one or more of polylactide, polyglycolide, poly(lactide-co-glycolide), poly-β-hydroxybutyrate and poly-β-hydroxyvalerate; b) is a hydrophilic polymer comprising polyethylene glycol; c1) is a first functional end group bound directly to and linking the hydrophobic polymer a) to the hydrophobic biodegradable polymer a); and c2) is a primary amino group, not bound to, but capable of covalently binding, a surface-modifying substance d) to the hydrophilic polymer b) by way of an at least bifunctional molecule, wherein the at least bifunctional molecule, when bound to the copolymer, has at least one free functional end group that is different from the second functional end group c2) and that is capable of covalently binding with the surface-modifying substance d), and wherein the structure of the copolymer permits binding the copolymer-linked bifunctional reagent to the surface modifying substance d)

without substantial loss of bioactivity of such substance in an instant reaction at room temperature with a solution or suspension comprising the surface-modifying substance d).

8. I also understand that claims 1-3, 5, 9, 10, 12-15, 33, 36-38, 41-44 and 67-74 have been rejected over Domb et al. (U.S. Patent No. 6,365,173; hereinafter "Domb") in view of Greenwald et al. ("Camptothecin-20-PEG Ester Transport Forms: the Effect of Spacer Groups on Antitumor Activity" Bioorganic & Medicinal Chemistry 6 (1998) 551-562; hereinafter "Greenwald"); and claims 1-3, 5, 9, 10, 12, 14, 15, 33, 36-38, 41-44 and 67-74 have been rejected over Hirosue et al. (U.S. Patent No. 6,254,890; hereinafter "Hirosue") in view of Greenwald.

9. Fact 1: In reference to (a) the drawing authored by the Examiner on page 3 of the FOA allegedly of a "block copolymer poly(L-lactide-b-ethylene glycol)" aka a PEG-PLA and (b) his contention on the Continuation Sheet of the AA that "[t]he artisan of ordinary skill would immediately recognize that these structures are the unique chemical structures associated with the named compounds" (emphasis added), it is a fact that they are not the only chemical structures associated with the named compound and thus are not the "unique" chemical structures associated with the named compound.

10. Fact 2: Moreover, such non-uniqueness was known in the art at the time of the invention, based upon my own information and belief, and furthermore based upon and evidenced by, for instance, the disclosures of Hirosue and Domb as outlined below.

11. Fact 3: Indeed, the fact of the matter is that there existed structure other than that drawn for the named compound. In other words, other chemical structures exist(ed) for PEG-PLA.

12. Fact 4: These other structures, as a matter of fact, exist(ed) in the context of being equally representative or substantially equivalent to the drawn PEG-PLA.

13. Fact 5: As with the preceding Fact 2, the characteristic of these other structures being recognized as equally representative or substantially equivalents of PEG-PLA was known in the art at the time of the invention, based upon my own information and belief, and based upon, for instance, the disclosures and my expert interpretations of Hirosue and Domb.

14. Fact 6: Domb and Hirosue each teach different structures of PEG-PLA.

15. Fact 7: Hirosue teaches a PEG-PLA with a free terminal carboxylic acid in Example 4, the terminal carboxylic acid being converted into an activated ester using N-hydroxysuccinimide for reaction with an amine to form an "amide". Therefore, Hirosue teaches the conjugation of the hydroxy group in PLA with the hydroxy group in PEG to form an ether linked PEG-PLA.

16. Fact 8: Domb, on the other hand, teaches the conjugation or linkage of the free carboxylic acid in PLA with a hydroxyl group in PEG to form an ester linked PEG-PLA. *See* Domb at column 4, line 20, to column 5, line 59.

17. Fact 9: Either of the two structures mentioned above for PEG-PLA, that is, either an ester linked PEG-PLA with a free terminal secondary alcohol as in Domb or, an ether linked PEG-PLA with a free terminal carboxylic acid, depending on whether the PLA and PEG are linked via a carboxylic acid or an alcohol in PLA, are/were known to be PEG-PLA in the art.

18. Opinion 1: First of all, as person of ordinary skill in the art, I would derive both of the Hirosue and Domb structures for PEG-PLA based upon the distinction in Fact 9. As an expert in the field, my opinion is that one of ordinary skill in the art also would have derived both of the two structures for PEG-PLA.

19. Opinion 2: Further, as one of ordinary skill in the art my interpretation of Domb and Hirosue is that they each teach different structures of PEG-PLA, and as an expert in the field my opinion is that one of ordinary skill in the art would have interpreted Domb and Hirosue as each teaching different structures of PEG-PLA, both interpretations of which further corroborate the deduction of Opinion 1.

20. Opinion 3: Therefore, the Examiner's contention/assertion in the AA that the artisan of ordinary skill in the art would immediately recognize that these structures are the unique chemical structures associated with the named compounds is simply not true.

21. Fact 10: Neither Domb nor Hirosue contain disclosure of or reveal a free amine terminated PEG-PLA.

22. Fact 11: Domb in fact discloses/reveals either an ionic, hydrogen or non-covalent bond between the carrier and the bioreactive.

23. Fact 12: Hirosue, as a matter of fact, discloses/reveals, at best, an amide bond, and not a free amine, formed between a free amine on a ligand and a free carboxylic acid group on the PEG-PLA using an activated ester such as N-hydroxysuccinimidyl ester of the PEG-PLA terminal carboxylic acid.

24. Opinion 4: In my capacity as an expert in the field and in my opinion on the thinking of one skilled in the art at the time of the invention, neither Domb nor Hirosue taught at the time of the invention or teach a free amine terminated PEG-PLA.

25. Fact 13: Domb and its combination set out by the Examiner do not disclose, reveal, teach or suggest a linear block copolymer of the type specified on pages 3-12 of the document dated March 22, 2010 of US App. No. 10/019,797, in which the free amine group is capable of covalently binding with a surface-modifying substance.

26. Opinion 5: In my opinion, under both of my "Opinion 4" capacities, Domb in fact is diametrically opposed to the invention defined in the present claims because it taught at the time of the invention and teaches that there is either an ionic, hydrogen or non-covalent bond between the carrier and the bioreactive, in contrast to the present claims in which the free amine group is capable of covalently binding with the surface-modifying substance.

27. Fact 14: Hirosue and its combination set out by the Examiner do not disclose, reveal, teach or suggest a linear block copolymer of the type specified on pages 3-12 of the document dated March 22, 2010 of US App. No. 10/019,797, in which a free amine is formed between a free amine on a ligand and a free group on the PEG-PLA.

28. Opinion 6: In both of my capacities, Hirosue taught at the time of the invention, and teaches, at the very best, that an amide bond, and not a free amine, is formed between a free amine on a ligand and a free carboxylic acid group on the PEG-PLA using an activated ester such as N-hydroxysuccinimidyl ester of the PEG-PLA terminal carboxylic acid.

29. Fact 15: Domb, Hirosue, and their combinations as set out by the Examiner, do not disclose, reveal, teach or suggest free primary amine terminated PEG-PLA compositions of the type specified on pages 3-12 of the document dated March 22, 2010 in the matter of US App. No. 10/019,797.

30. Opinion 7: It is therefore my opinion that Domb and Hirosue, taken in the combinations set out by the Examiner, do not disclose, reveal, teach or suggest the free primary amine terminated PEG-PLA compositions of the presently claimed invention.

31. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements may jeopardize the validity of the present application or any patent issuing thereon.

Respectfully submitted,

Date: 21st June, 2010

Jayasree Vasudevan

Jayasree Vasudevan, Ph. D.